Episode 27 Transcript: Understanding sepsis, its detection and treatment strategies

Andrea Ott-Vasconi:

I'm Andrea Ott-Vasconi, and welcome to Ortho Science Bytes. Today, I'm joined by Dr. Lui Forni. Dr. Forni is a professor and consultant nephrologist and intensivist at Royal Surrey County Hospital NHS Foundation Trust in Guildford, England. Professor Forni earned a PhD in physical chemistry, and subsequently studied medicine, specializing in nephrology and intensive care medicine. His research interests include preoperative assessment of high-risk surgical candidates, renal replacement therapy, diagnosis, pathophysiology and treatment of acute kidney injury and predictive modeling in acute medical admissions. He lectures both nationally and internationally and has published widely. He served as the past research chair and is the current secretary of the European Society of Intensive Care Medicine. Thank you, Dr. Forni for joining me today for a discussion on the topic of sepsis. Let's start with defining what sepsis is and is not as this is often not well understood. It is not a disease, and it is not an infection. Tell us more about what sepsis is, and how it can occur.

Dr. Forni:

Well, thanks, Andrea. Thanks for that rather grand introduction. Whenever I hear things like that, I'm struck by imposter syndrome, but I can assure you that I'm not an impostor. So, sepsis is something we've all heard about and certainly from a lot of the media attention it's had over the last two decades, something that we're very aware of. And it's simplistically described as life threatening organ dysfunction caused by dysregulated host response to infection.

Dr. Forni:

So, what does that actually mean? Life threatening organ dysfunction is what doctors like me who work in critical care deal with, and so that's where our organs begin to fail. And by that we include the brain, we include the heart and the lungs. We include the kidneys, and we include the gut and the liver, as well as the bone marrow and skin. So all our organs are affected by this dysregulated host response. So it's not the same as a bacteremia or an infection where you have infection with a bacteria or a virus, for example, that the body can deal with normally. This is a dysregulated response, so it's almost like the immune system has gone mad and attacks the organs as well as attacking the infected organism that started the infection off.

Dr. Forni:

And so, it's not a particular diagnosis. It's not like pneumonia is defined by changes in x-ray or whatever, or multiple sclerosis. It's defined by various features. In sepsis, we have a constellation of symptoms and signs which group together form this syndrome of sepsis. So another way of looking at it, this dysregulated response, is if we just take bacteria in the bloodstream, if we brush our teeth around 20% of us will have bacteria in our bloodstream after brushing our teeth. I don't want you to be alarmed by that because it's far better for you to brush your teeth than to ignore it. But that bacteremia is nonpathogenic, right? So we can deal with that quite easily and the bacteria get killed, and we don't have to worry about it. But in conditions leading to sepsis, we have an infection which triggers this chaotic response which can lead to organ dysfunction and if not treated ultimately death.

Andrea Ott-Vasconi:

And who is at risk of getting sepsis?

Dr. Forni:

So it's important to realize the global burden of sepsis because we kind of sit here, me in the UK and you in the States, and we tend to think of just of our own micro environment really. But the global burden is huge. I mean there are over 50 million cases of sepsis a year globally. And last data counted about five years ago pre-COVID, there was about 11 million deaths a year from sepsis, and that's about one in five of all deaths. So one in five of all deaths across the globe are due to sepsis. And within that group about half are children. So children are at increased risk of sepsis and of course, this is really in low and middle income countries. In the higher income countries, then also the elderly are at higher risk or are more obviously at higher risk. And so at both ends of the age spectrum are individuals that are at higher risk, but also pregnant individuals or recently pregnant women are at higher risk.

Dr. Forni:

Patients in the hospital are at higher risk, mainly because they're having things done to them. You don't happen to go to the hospital just for fun. Patients in ICU again because we're doing lots of things to patients so they can get infected. People with incompetent immune systems, immune systems that don't work properly, so HIV and AIDS for example, people with liver disease, people with cancer, people with kidney disease, and then autoimmune diseases as well. These are all at risk of sepsis. And the other group that some of you may know, individuals with no spleen, people who have had a spleen removed from trauma, for example, or from another condition that are quite often supposed to take regular prophylactic antibiotics. And so people without spleen are at higher risk of getting sepsis. And so what you then might want to ask yourself is, well, why is it, right?

Dr. Forni:

So why are children at higher risk and why are the elderly at higher risk? Well, part of that is because our immune system is not the same at day naught as day 80. So our immune system takes time to develop and our immune system is not fully developed by adolescence. So it takes some time for our immune system to learn. And you may be aware that there are two types. That the immune system is described as having two components, the innate immunity, so that's the immunity that we're kind of given by our mothers and fathers. So this is our first line of defense, the innate or nonspecific immune response. And this is cellular reactions and chemical reactions and defenses against pathogens and bacteria for example. So the main purpose of this part of the immune system is to immediately prevent the spread and movement of foreign bacteria, for example, throughout the body or anything that's recognized as foreign.

Dr. Forni:

And so that includes the white blood cells that we know about macrophages, neutrophils as well as dendritic cells, mast cells, basophils, eosinophils. And then we have our second line of defense, the adaptive immune response. So this is acquired immunity or specific immunity, interestingly only found in animals with backbones. So it's only found in invertebrates. And it's specific to actually the pathogen presented. So what does that mean? Well, a good example is chickenpox, right? So if we get vaccinated against chickenpox, then our adaptive immune system learns what chickenpox looks like. This is the T and B lymphocytes. And then when we come across the chickenpox virus, we get rid of it. So we've learned through vaccination what to do with it. Our bacteria that we get from brushing our teeth are innate or nonspecific system gets through that straightaway. That's foreign gets rid of it. So they're a lot like the attack troops that come bounding in.

Dr. Forni:

So if we look at children, a child's immune system is very different from adults in terms of both innate and adaptive function. As I said, it's adolescence before our immune system has matured. If you think about babies being born, they come from a sterile intrauterine environment and then suddenly they're out there being exposed to all these microbiological insults. And some of them particularly neonates, are profoundly immunocompromised because they haven't had time to develop a part of their innate and certainly not adaptive immune response. So adaptive immunity particularly is suppressed in the very, very young. Even though T-cell responses may be high, the immune system hasn't learned yet.

Dr. Forni:

So put simply, the immature response of the immune system makes the children more prone to infection. And because they are more prone to infection, then they're at higher risk of developing this chaotic response, which can also follow in infection. Now, if we look at the elderly, it's almost the reverse of that. We get immune senescence. So in the same way that when we're over 21, to put it politely, we can't run as fast as we could when we were 18. Similarly, our immune system can't work quite as well, and we see a falloff in both innate and adaptive immunity. So both these put us at higher risk of infection and by its very nature then at higher risk of this dysregulated host response. So you can still get this dysregulated response despite the fact that you're more prone to infections, kind of a double-edged sword really.

Andrea Ott-Vasconi:

Thank you for helping us understand the reasons why especially the children and elderly are at greater risk of getting sepsis. What are the warning signs of sepsis for those who might have a local infection like an infected cut or pneumonia who may be receiving care at home?

Dr. Forni:

Well, good question, Andrea because it's sepsis can be easily missed. And you have to have what doctors call a high index of suspicion for sepsis. So if someone comes in with an infection, there are certain things we would look for and some of these things are easily applied at home. So in the States the Sepsis Alliance have pushed this, the so-called "It's About TIME", the TIME acronym, so watch for changes in **temperature** like high or low, evidence of an obvious **infection**. So that may be a skin infection, for example, or maybe a productive cough, a chest infection, change in **mental** status that's actually quite important. And for any of you who have been unfortunate enough to have a child who has become ill, you'll see that quite often. The kids become quite floppy and unresponsive, and generally **extremely ill.** So that's the **TIME.** It's temperature, infection, mental decline, extremely ill.

Dr. Forni:

In the UK, we have **SEPSIS**, and so that's similar. So slurred speech, again showing the effects on the central nervous system and the brain, extreme sweating, passing no urine, severe breathlessness, that's not only because of infection in the chest, it can be other reasons. So that's SEPSIS, right? **Slurred speech, Extreme sweating and shivering, Passing no urine, Severe breathlessness**, and **It** feels like the patient's going to die. So there's a sense of impending doom particularly in adults, and then **Skin** may be mottled, or clammy. So symptoms like this, an infection or it may have been an infection such as a chest infection, which seems to not be going away and developing other signs. So at home they're the kind of things that if you're getting into that ballpark, you really need to see a doctor pretty quickly. So either think of **TIME** or **SEPSIS,** and there are lots of other tools for looking at that.

Andrea Ott-Vasconi:

Thank you. Those are very important to remember and signs to look out for. And there's also the risk that hospitalized patients can acquire an infection during their stay, which can then develop into sepsis. What measures do hospitals take to prevent sepsis from occurring?

Dr. Forni:

Yeah, well, again, that's an excellent point. And one of the other risk factors of sepsis, of course, is having had a hospital stay. So there's been lots of studies that have looked at patients who have recently been in hospital and then represent. And so that's another thing that should be also viewed as a risk factor, recent hospitalization. So an obvious example of that might be a wound infection after surgery. So part of the problem, as I alluded to earlier, when going into hospital is doctors and nurses do stuff to you. So either operations or intravenous cannula or taking blood or putting in urinary catheters. And so, there are lots of instances where our immune system is challenged by foreign bodies, which can be portals to infection. And so we have lots of things in place to look for that. So for example, cannula, which are the plastic tubes in veins where we administer drugs are viewed daily by nursing staff.

Dr. Forni:

And our notes are made as to the appearance of the skin, but also how long these things have been in. And hospitals will have various protocols for changing these cannulae. There's something called the Matching Michigan program, which was a program brought into intensive care units where doctors, particularly doctors who were placing intravenous cannulae were viewed by nurses and they had a checklist which had to be followed. And if it wasn't, then the procedure would be abandoned, had to be started again. And introduction of such protocols, reduced line or catheter mediated sepsis dramatically. Urinary catheters, for example, we try not to put them in and if we do, they're put in Foley catheters as they are known in the US. We try to get them out as soon as possible.

Dr. Forni:

The other thing is of course, that patients come into hospital may have multi-drug-resistant organisms. These are organisms that defy the use of our modern-day antibiotics, and these individuals tend to be cohorted. And so we will have patients with methicillin-resistant staphylococcus aureus MRSA placed in isolation rather than being over wards. So there are various protocols and things that are in place to try to minimize hospital acquired infections.

Andrea Ott-Vasconi:

And we know that when sepsis occurs, it is a medical emergency that requires immediate response. What surveillance measures are used to rapidly detect its onset?

Dr. Forni:

So in the higher income countries, we have a fairly impressive armamentarium in terms of what we can employ to rapidly detect the onset of sepsis or to survey patients for that. And so are probably obvious the things I've discussed such as temperature shivering or whatever. So the clinical signs, there are other things that we would measure that you might not necessarily measure at home. So simple things like heart rates. And so in profound sepsis or septic shock, the heart rate can be very high and interestingly in younger adults it might be high but not quite as high as you might expect. And so anything over a hundred should be viewed certainly with suspicion, a falling blood pressure. And some of those can be coincide with reduction in mental status. But then we have our blood tests and blood investigations that

we look at. So there's rapid point of care analysis that the patient can be exposed to for one of the better words.

Dr. Forni:

So we'll look at arterial punctures and we'll look at the amount of oxygen in the blood, the pH, that's the acidity of the blood, and also measure something called the lactate. The lactate is a reflection of our body changing its type of metabolism as we search for a fuel to fight infection. And that has been shown to be raised and an indicator of poor outcome in patients with sepsis. And then we had the more classical blood tests. So white cell count for example, can be elevated that's in your CBC or full blood count we call it in the UK. So white cell count may be raised and neutrophil count, which is part of the innate immune system may be elevated. And then we have things like Capsular Reactive Protein, the CRP, that's a test if that's raised that would also increase the index of suspicion of someone having sepsis.

Dr. Forni:

Then there are other tests which we tend to group together. It's things like biomarkers and procalcitonin for example is a test that's becoming increasingly available, which should be related to bacterial infection. And that's particularly useful sometimes if we're trying to differentiate between viral and superadded bacterial infection. So in COVID, for example, the COVID outbreak, a lot of hospitals that weren't using procalcitonin adopted that very quickly to try and help in the management of patients with COVID to determine whether their clinical state was due to viral sepsis or whether it was what we call a superadded or a bacterial infection on top of the virus, which we did see particularly in intensive care patients. So we had quite a range of tools ranging from the fairly basic, fairly routine, to the more advanced.

Andrea Ott-Vasconi:

Once sepsis is detected, how is it treated and thereafter monitored?

Dr. Forni:

There's lots of talk about golden hours of treatment and things like this, but the mainstay of treatment is timely, appropriate antibiotics. And so trying to nail down the fact that sepsis is present is quite important because we live in an era of as I mentioned, multi-drug resistance and antibiotics are precious. There aren't hundreds of them in the pipeline being developed. And so, we have to have sensible antibiotic husbandry. And by that, I mean, we need to identify patients with sepsis and treat them early and appropriately. And so, it may be that we use broad-spectrum antibiotics early on. And then when we get more detailed information as to the pathogen affecting the individual and the specificity of antibiotic action against that organism, that we can tailor our treatment specifically. And in fact, this is an area that's growing in terms of rapidity of testing. So we used to have to take blood cultures, you would go to a laboratory and about five days later or so we would get a result back saying it's a haemophilus, for example, and these are the sensitivities to these antibiotics.

Dr. Forni:

Well, that many days down the line, we've already treated the patient, there are now lots of tests that can give us an idea within six to eight hours of what bugs are present and whether they're what they may be susceptible to. So early use of antibiotics and then tailor it to the individual is actually very important. And by doing that, we may well limit the production of multi-drug resistant species where

they're exposed to antibiotics that they're not particularly susceptible to but can then develop resistance. So antibiotics are the mainstay, but we have to bear in mind those caveats in terms of resistance. The other things, of course, we've all been surrounded by COVID-19, the COVID virus, and we've seen viral infections also can lead to sepsis. And of course, antibiotics are of no use against viruses. So in those cases, we need antiviral medicines or things that might modulate the immune response.

Dr. Forni:

And so as we all know, there was no initial treatment for COVID. Antivirals are not so prevalent. And that area is developing again with refashioning of older drugs to see if we can get more antivirals. But again, the same thing holds that treating viral infections with nonspecific antibiotics is a recipe for longer term disaster in my opinion. So we have to be careful, we have to be able to differentiate between viral and bacterial infections. And then the other thing to do is make sure we give adequate courses of antibiotics, but not carry on regardless for weeks and weeks. And there are situations where there can be the case, but we can use some of our tests like procalcitonin, for example, to tailor when we may stop our antibiotic use. So tests can be used not only to identify patients, also guide treatment, and in fact tell us when to stop treatment.

Andrea Ott-Vasconi:

Let's talk more about the impact of sepsis on the organs and more specifically sepsis associated acute kidney injury. You talked about the use of antibiotics. We know for instance that they can also be nephrotoxic. So how can sepsis and the treatments use to manage sepsis negatively impact the kidney?

Dr. Forni:

Yeah, it's such a double-edged sword, because a lot of the drugs we use, as you pointed out, Andrea can affect the kidneys themselves, particularly some antibiotics. And so we don't want use those where we don't have to, but also we know that some of the antibiotics that are nephrotoxic we can measure levels to make sure that patients are not being exposed to toxic levels of the antibiotics. The effect directly on the kidneys is interesting, and we have to consider some of the things that trigger off the whole sepsis cascade. So there are various molecular patterns that we can see within individuals, the so called DAMPs and PAMPs. So, what are we talking about here? Well, PAMPs are pathogen associated molecular patterns, right? So these are patterns that released following bacterial infection, for example, and then destruction of the bacteria. So leading to these molecular patterns, which in themselves may trigger more dysregulated activation of the immune system.

Dr. Forni:

And then, also these DAMPs, damage-associated molecular patterns, which actually come from our own cells and tissues. So when our knights in shiny armor or our innate immune system rush out and start smashing into the bacteria releasing PAMPs they can also damage our own tissues, leading to this DAMPs profile dysregulated activation of the immune system. And there are various things that each individual has that may predispose them to such a reaction. So, what's interesting there is that you and I, Andrea got forbid, but we may be infected by the same bacteria and one of us may have a much more profound response leading to sepsis than the other. And that's this background susceptibility, which is affected not only by basic comorbidities but also genetic variants.

Dr. Forni:

And this inherent susceptibility is a key contribution to tissue injury. Now, what happens in the kidney is that we can get cellular infiltration and damage to the kidney per se. We can also get damage from the PAMPs and DAMPs directly, directly affecting the kidneys. But we can also see the results of the other effects of sepsis. So for example, a fall in blood pressure, a fall in blood pressure leads to a reduction in perfusion of organs that includes kidneys. Now, that means, that the kidneys don't get a blood, an adequate blood supply, don't get an adequate amount of oxygen, so cannot function effectively. And this can be detected in certain cases early on by looking at more specific tests.

Andrea Ott-Vasconi:

And what can be done to prevent acute kidney injury. You mentioned some specific tests and also prevent long-term complications that result from acute kidney injury such as chronic kidney disease or renal replacement therapy.

Dr. Forni:

So that's an area that's opened up with time. As intensive care doctors particularly or critical care doctors we're always very obsessed with the patient in front of us, getting the patient better and getting out of the ICU and that's our job done. Whereas in fact, it's really the start of our job because we want to make sure that the patient who leaves intensive care will eventually get back to being what they want to be. So going back to work or going back to being a valued member of their community. And in order to do that, we've got to make sure that we can try and prevent longer term complications. So for example, patients with acute kidney injury may progress to chronic kidney disease, eventually to end stage kidney disease on the dialysis program. So we want to try and avoid that. Now, in terms of early markers of kidney damage, there are tests available.

Dr. Forni:

One of them is the NephroCheck*, which I've worked on as well as many others, that's a combination of two of these biomarkers. These are markers found in the urine early on in acute kidney injury. Now, one of the points I did stress in sepsis is early identification, and then appropriate treatment. And the problem with acute kidney injury is that the tests we have for monitoring it, take some time to change. So we have a measure in a blood serum creatinine that takes 24 to 48 hours for it to go out of the normal range or to increase to a level where we might consider patients got an acute kidney injury. Urine output is slightly more easy to look at if we're monitoring. And that's why one of the things in the TIME and SEPSIS as mentioned earlier was talking about lack of passing urine, but not all patients are aware of that or may pass some urine.

Dr. Forni:

Now, if we examine the urine for these biomarkers, we can see evidence of cell cycle arrest or cell stress, early on in the course of disease. So what could we do in a patient with suspected sepsis and positive biomarkers? Well, some people will say, "Well, we just treat the sepsis." Yes, that's true, but we also optimize the background for the kidney, if you like. So we'll make sure there's appropriate profusion pressure for the kidney, as I talked about, blood pressure may be low or we correct that, the fluid balance, we may give fluids to the patients with acute kidney injury early and in a targeted fashion. You may ask why you need that, well the problem’s in sepsis with its dysregulated response, we tend to lose fluid within the vascular compartment. We need to make sure that's maintained, and that adequate perfusion is maintained to the kidney.

Dr. Forni:

So we limit exposure to poisons, and we make the environment as healthy as possible for normal renal function. At the moment, that's about it. There are a few other fancy tests, but there are new molecules in the pipeline. And hopefully, if we have this conversation in 10 years' time, there'll be significant differences. There are certain drugs undergoing tests as we speak in sepsis associated kidney injury, which may show a reduction in time, but these are early pilot data was interesting, but we have to wait to see if that's verified in larger randomized control trials. So at the moment, individualized treatment in terms of blood pressure, volume, antibiotics, early detection with things like biomarkers, and then hopefully in the future specific targeted therapies.

Andrea Ott-Vasconi:

Thank you for all the research that you're doing, particularly in the field of sepsis associated AK,I a very important work. And thank you so much for the insightful discussion today on this very important topic of sepsis. I hope everyone enjoyed this podcast episode. Make sure to review sections within the podcast description with suggested reading materials, links to learn more about sepsis, and a summary of the key takeaways from this episode. Based on today's podcast, I'll leave you with our pop quiz. Which tests are commonly used to detect sepsis? You can go back and listen again if you'd like some more detail. Thank you so much for listening today. Please subscribe to Ortho Science Bytes our monthly podcast where we'll be discussing more complex questions, we face every day in our labs. Brought to you by Ortho Clinical Diagnostics, Pioneering Advances and Diagnostics for 80 years because every test is a life. Take care, stay healthy and safe.

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